REMARKS

Claims 1-6 are pending in the instant application. Claims 1-6 have been rejected. Claim 1 has been cancelled. Claims 2, 3 and 6 have been amended to place them in condition for allowance or appeal. These amendments do not introduce any new subject matter, and support for them can be found in the specification. After entry of this amendment, Claims 2-6 will remain pending.

Rejection of Claims 1-6 under 35 U.S.C. §103(a)

The Examiner has maintained the rejection of Claims 1-6 under 35 U.S.C. §103(a) over Breslin et al., US Patent No. 7,234,580 ("the '580 patent"), and Arrington et al., US Patent Application No. 10/517,559 ("the '559 application"), in view of Patani et al., *Chem. Rev.*, 1996, Vol. 96, pp.3147-3176 ("Patani et al."). Specifically the Examiner states:

> ...the Examiner finds the instantly claimed invention is *prima facie* obvious over the '580 patent, and the '559 application in view of the Patani's teaching, because the Patani reference do provide the motivation for one of ordinary skilled [sic] in the art to modify the prior art teachings for the instantly claimed invention, namely replace –H with –F on the very closely related prior art compound...
>
> ...the '580 patent and the '559 application do suggest that the pyrrolidine ring as R^c can be further optionally substituted with R^{11}, wherein R^{11} as halo...

Applicants respectfully traverse this rejection. However, Applicants have cancelled Claim 1, and amended Claims 2 and 3 such that the scope is narrower.

Although the '580 patent and the '559 application suggest heterocyclyl rings which may be substituted with many substituents, including halo, neither reference teaches nor suggests the pyrroline rings with the substitution patterns claimed in the instant application.

In fact, substitution at the four position with a fluoro group unexpectedly results in a favorable profile when compared with unfluorinated analogues and analogues containing fluorines in other positions. Data supporting these unexpected properties can be found in an accepted manuscript that will be in print shortly, "Cox, Christopher D., et al., "Kinesin spindle protein (KSP) inhibitors. Part 9: The discovery of KSP inhibitor MK-0731 for the treatment of taxane refractory cancer," J. Med Chem, Vol. XX, pages XX-XX (copy enclosed). Cox, et al.

demonstrates these unexpected and favorable results with close analogues (piperidine instead of pyrrolidine).

As explained in Cox, et al. on page 8, the unfluorinated analogue, Compound **11** (structure shown on page 56), has an undesirable Pgp profile. Since **11** is a Pgp substrate, it is efficiently effluxed from cells by Pgp as indicated by its multi-drug resistance (MDR) ratio, a measure of Pgp-mediated resistance to mitotic arrest that has recently been reported to be a reliable high-throughput approach to measure Pgp-susceptibility of KSP inhibitors. The MDR ratio is calculated by dividing the IC_{50} for induction of mitotic arrest in a cell line that highly overexpresses Pgp by the IC_{50} in the parental line that does not express Pgp. An MDR ratio of unity indicates that the KSP inhibitor is not effluxed by Pgp because it is equipotent in both cell lines. As a measure of comparison, Taxol® has a ratio of greater than 25,000, since it is devoid of activity in the overexpressing cell line. Compounds with a ratio less than 10 are acceptable for development, but **11** has a ratio of 21, with an EC_{50} of only 150 nM in the Pgp-overexpressing cell line.

As further explained in Cox et al. on page 9, careful modulation of the amine basicity allows the balance of Pgp efflux potential (as measured by the MDR ratio) with KSP potency. Addition of a fluorine was found to modulate the amine basicity; however, the placement of fluorine is critical to the desirability of the compound. Compound **14** (structure shown on page 56),which has a fluoroethyl amine group, demonstrated a promising overall profile, including excellent in vivo activity (EC_{90} = 100 nM), good formulation properties, and the potential for suitable pharmacokinetic parameters. However, it proved to be toxic; N-dealkylation of the piperidine ring occurs in vivo, causing the formation of fluoroacetate as a byproduct, a known toxin with acute pharmacology.

Placement of the fluorine in a strategic, metabolically benign location on the piperidine ring allowed simultaneously avoidance of toxic metabolite formation and provided an optimized in vitro and in vivo profile. For example, Compound **30** (structure shown on page 57) displayed superior potency in both the enzymatic KSP assay and a cell-based assay, and does not result in the formation of the toxic fluoroacetate byproduct. Importantly, **30** also has significant activity in Pgp-overexpressing cells, with potencies of 4.2 and 18.9 nM in the parental and Pgp-overexpressing cell lines, respectively, resulting in an MDR ratio of 4.5. For comparison, the corresponding values for Taxol® are 0.5 nM and > 10 μM. Thus, **30** has the ability to induce a mitotic block with an IC_{50} of 19 nM in cells that are refractory to Taxol® due to Pgp-overexpression.

In light of these amendments and arguments, Applicants respectfully request the rejections of Claims 1-6 under 35 USC §103(a), be withdrawn.

Rejection of Claims 1-14 and 18 for Double Patenting

The Examiner provisionally rejected Claims 1-14 and 18 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over US Patent No. 7,235,580 ("the '580 patent"). Applicants respectfully traverse this rejection. Applicants have cancelled Claim 1 and amended Claims 2 and 3; accordingly, the '580 patent does not contain any species that overlap with the instant application. Furthermore, Applicants have addressed the obviousness assertion in the previous paragraphs. Accordingly, Applicants respectfully request that this rejection be withdrawn.

If a telephonic communication with the Applicants' representative will advance the prosecution of the instant application, please telephone the representative indicated below. Applicants believe no additional fees are due but the Commissioner is authorized to charge any fees required in connection with this response to Merck Deposit Account No. 13-2755.

Respectfully submitted,

By 

Nicole M. Beeler
Reg. No. 45,194
Attorney for Applicants

MERCK & CO., INC.
P.O. Box 2000
Rahway, New Jersey 07065-0907
(732) 594-1077

Date: June 10, 2008